Product Circular
for
Pooled Plasma, Solvent/Detergent Treated
VIPLAS/SD™

DESCRIPTION

Pooled Plasma, Solvent/Detergent Treated - VIPLAS/SD™ is a sterile, pooled human plasma preparation treated with the solvent, tri(n-butyl)phosphate (TNBP), and the detergent, Triton X-100. VIPLAS/SD is intended for intravenous administration for those indications for which FFP is indicated[1] (see INDICATIONS AND USAGE).

VIPLAS/SD is prepared from ABO blood group type-specific units of human plasma which are frozen so as to preserve their content of labile coagulation factors. The product is derived from blood collected from volunteer donors. The frozen plasma units are pooled into lots containing no more than 2,500 donations, thawed, and treated with 1% TNBP and 1% Triton X-100 (SD reagents) for four hours at 31°C. The SD reagents are removed by vegetable oil extraction followed by reverse-phase chromatography on a C18 column. The VIPLAS/SD is then sterile filtered into blood bags at standardized, 200 mL, volumes and refrozen.

The SD viral inactivation technology used for VIPLAS/SD is similar to that used in the preparation of numerous other plasma products including coagulation factor concentrates used for the treatment of persons with hemophilia[2]. The SD treatment has been shown to be capable of significant inactivation of lipid-enveloped viruses with killing of lipid-enveloped viruses typically observed within the first 15 minutes of the four-hour treatment time. However no procedure has been shown to be totally effective in removing viral infectivity from plasma-derived products. Accordingly, the benefits and risks of treatment with this product should be carefully evaluated before use.

Studies of viral inactivation have been performed with human pathogenic viruses as well as laboratory viruses which are models of human disease including Sindbis virus and bovine viral diarrhea virus (BVDV), which are models for hepatitis C virus (HCV). Table 1 illustrates the viral inactivation characteristics of the SD process for a broad spectrum of lipid-enveloped viruses.

TABLE 1: *IN VITRO* ELIMINATION OF VIRAL INFECTIVITY BY SD TREATMENT

Virus	Elimination (log_{10})
VSV (vesicular stomatitis virus)	≥5.7 $TCID_{50}$*
Sindbis virus	≥5.7 $TCID_{50}$
HBV (hepatitis B virus)	≥6.0 CID_{50}**
BVDV (bovine viral diarrhea virus)	≥6.1 $TCID_{50}$
HCV (hepatitis C virus)	≥5.0 CID_{50}
HIV	≥6.0 $TCID_{50}$

*=tissue culture infectious dose **=chimp infectious dose

The SD process for virus inactivation has been shown not to alter or inactivate labile coagulation factors nor to alter or inactivate other plasma proteins such as fibrinogen and immunoglobulins[3,4].

VIPLAS/SD, contains not less than 0.7 units/mL each of factor V, factor VII, factor X, factor XI and factor XIII and not less than 1.8 mg/mL of fibrinogen. The prothrombin time and the partial thromboplastin time are not affected by the processing. VIPLAS/SD contains no leukocytes, and lacks the largest von Willebrand factor multimers. VIPLAS/SD contains no more than 3 µg/mL (ppm) each of TNBP and Triton X-100.

CLINICAL PHARMACOLOGY

VIPLAS/SD contains both labile and stable coagulation factors in amounts similar to those in FFP, as well as the other proteins present in plasma. VIPLAS/SD lacks the largest vWF multimers.

Coagulation factor persistence in plasma

Data on persistence in the circulation after infusion of VIPLAS/SD Pooled Plasma, Solvent/Detergent Treated have been obtained for coagulation factors V (3 patients) and X (1 patient) in patients congenitally deficient in these factors. In each case, factor levels determined after a 12-24 hour period were consistent with the information available in the literature regarding the half-life of each factor[5].

Prophylaxis in patients with congenital factor deficiencies

Management of bleeding was evaluated in the surgical setting. In 34 of 35 factor-deficient patients receiving 46 infusions of VIPLAS/SD for surgical prophylaxis, results from 25 patients (32 bleeding episodes) show that administration of a dose of 15 mL/kg resulted in an increase of 77 mg/dL fibrinogen, 0.13 units/mL of factor V, 0.15 u/mL of factor VII, and 0.24 u/mL of factor XI. Hemostasis was maintained during the surgical period in 40/46 infusions. Bleeding in the remaining six episodes was judged to be due to inadequate dosing or occurred in the late post-operative period. Surgeries successfully performed included dental surgeries, lumbar disc surgeries, exploratory laparotomies, abdominal hysterectomies and oophororectomy, coronary artery bypass grafts and valve replacements, arthroscopic surgeries, parathyroid exploration, transuretheral prostatectomy, facial plastic surgery, cholecystectomy, and removal of a meningioma.

TABLE 2: INCREASE IN COAGULATION FACTORS IN PATIENTS RECEIVING VIPLAS/SD FOR SURGICAL PROPHYLAXIS

Coagulation Factor	No. of Episodes	No. of patients	Observed Increase per Infusion of 15 mL/kg (mg/dL or u/mL)			Average % Recovery
			Average	Low	High	
Fibrinogen	2	1	76.6	66.9	86.3	109%
Factor V	6	4	0.13	0.09	0.17	72%
Factor VII	5	4	0.15	0.08	0.22	66%
Factor XI	19	16	0.24	0.10	0.53	94%

Factor XIII deficiency is a rare condition in which patients require approximately monthly transfusions with FFP in order to preclude bleeding. Four patients with congenital factor XIII deficiency were treated prophylactically with 1-2 units of VIPLAS/SD every 21-40 days on average for a period of 2 to 15 months, and each remained asymptomatic. A fifth factor XIII-deficient patient was successfully treated for soft tissue hemorrhages on an on-demand basis.

Treatment of actively bleeding patients with congenital factor deficiencies

Eleven patients with congenital factor deficiencies (factors I, V, X, XIII) were treated for 50 episodes of active bleeding, with an average dose of 4.7 units of VIPLAS/SD per episode. Of twenty episodes where the patients had coagulation function measured prior to transfusion, nineteen episodes had documented abnormal PT and/or aPTT levels prior to transfusion, and all showed a substantial shortening following infusion of VIPLAS/SD. Control of bleeding was achieved in all 50 episodes using VIPLAS/SD. Bleeding episodes that were successfully managed included head trauma, and bleeding into soft tissues, muscles and joints.

Urgent reversal of warfarin therapy

Seven patients who required urgent reversal of warfarin therapy during ten treatment episodes were treated with 52 units of VIPLAS/SD. For minor bleeding episodes or minor surgeries, 2-7 units of VIPLAS/SD successfully reversed the warfarin effect. For major surgical procedures, administration of 11-15 units of VIPLAS/SD successfully reversed the warfarin effect.

Treatment of patients with multiple coagulation deficits

Forty-five patients of an anticipated 150 were enrolled in a randomized, blinded study of patients with a prolonged prothrombin time. Approximately half of the patients were treated for warfarin toxicity, and approximately one third of the patients had exacerbations of chronic liver disease. Seven of 22 (32%) of the VIPLAS/SD-treated patients and 6 of 23 (26%) of the FFP-treated patients corrected their PT to 15 seconds or less after one infusion. For actively-bleeding patients, bleeding was controlled in approximately one third of the patients with either treatment. Treatment as surgical prophylaxis was more successful, with approximately 90% of patients in each treatment group being categorized as treatment successes. The study was underpowered to detect a difference between VIPLAS/SD and FFP should such a difference have existed.

Treatment of Chronic and Acute Thrombotic Thrombocytopenic Purpura (TTP)

Six patients with chronic TTP were treated with 0.5-3 units of VIPLAS/SD given at approximately 21-day intervals, with successful prevention of symptoms for the 6 consecutive cycle followup period.

Twenty-six patients with acute TTP were enrolled in a blinded, randomized study comparing VIPLAS/SD (N=16) to FFP (N=10). Of the 23 evaluable patients, the mean (± S.D.) volumes per treatment were 2,515 (±991) mL for the VIPLAS/SD- treated patients and 2,649 (± 742) mL for the FFP-treated patients. The mean number of exchanges for the VIPLS/SD-treated patients was 10.3 (± 6.8), compared to 9.7 (± 9.3) for the FFP-treated patients, and the total volume infused per patient was 28,523 (±22,417) mL for the VIPLAS/SD patients compared to 22,973 (± 16,443) mL for the FFP patients. Although no differences were detected between the groups in terms of survival, mean number of remissions per patient, number of relapses per patient or the number of patients achieving remission, the study was underpowered to show equivalence of the two treatments for the treatment of acute TTP.

INDICATIONS AND USAGE

The indications for use of VIPLAS/SD, Pooled Plasma, Solvent/Detergent Treated, are limited and include: treatment of patients with documented deficiencies of coagulation factors for which there are no concentrate preparations available, including congenital single-factor deficiencies of factors I, V, VII, X, XI and XIII, and acquired multiple coagulation factor deficiencies; reversal of warfarin effect; and treatment of patients with thrombotic thrombocytopenic purpura (TTP).

VIPLAS/SD is not indicated when coagulopathy can be corrected more effectively with specific therapy, such as vitamin K, antihemophilic factor (factor VIII) concentrates or other coagulation factor concentrates.

VIPLAS/SDis not indicated as a volume expander when blood volume can be safely and adequately replaced with other volume expanders.

PEDIATRIC USE

In the U.S. clinical trials, 1 neonate and 24 children (aged 2 months - 17 years) were treated for congenital factor deficiencies (16 patients), chronic TTP (5 patients), acute TTP (1 patient) and hepatic disease (3 patients). Duration of treatment ranged from 1 day to 51 months (median - 13 months). The expected efficacy was achieved in all patients, and no unusual or unexpected toxicities were seen.

CONTRAINDICATIONS

VIPLAS/SD contains the immunoglobulin IgA and should not be given to patients with antibodies to IgA or selective IgA deficiencies.

WARNINGS

The patient and physician should discuss the risks and benefits of this product.

As with any intravenous protein product, there is a possibility of an allergic-type hypersensitivity reaction to VIPLAS/SD. If anaphylactic or severe anaphylactoid reactions occur, discontinue infusion immediately.

VIPLAS/SD **is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. Prescribed manufacturing procedures utilized at the plasma collection centers, plasma testing laboratories and the manufacturing facility (including SD treatment) are designed to reduce the risk of transmitting viral infection. Despite these measures, such products may still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. ALL infections should be reported directly to your physician and V.I. Technologies, Inc. (through Infotrack) at 1-(800) 535-5053.**

Information for the Patient

Because SD treatment does not inactivate viruses which do not have a lipid envelope, there is a small but finite risk that parvovirus B19 or hepatitis A virus might be present in this product. Recipients of VIPLAS/SD at a typical dose of 10-15 mL/kg will receive approximately 6,000-9,000 mg of IgG and 480-1800 IU of anti-HAV per dose. This quantity exceeds that which is recommended for HAV prophylaxis when administered as an intramuscular gamma globulin preparation[6]. For chronic users of blood products, the recommendations of the National Hemophilia Foundation should be followed, and such patients should be prophylactically immunized against Hepatitis A.

Parvovirus B19 most seriously affects pregnant women or immune-compromised individuals. Symptoms of parvovirus B19 infection include fever, drowsiness, chills and runny nose followed about two weeks later by a rash and joint pain. Evidence of hepatitis A may include several days to weeks of poor appetite, tiredness and low-grade fever followed by nausea, vomiting and abdominal pain. Dark urine and a yellowed complexion are also common symptoms. If these symptoms appear, consult your physician.

PRECAUTIONS

Pregnancy Category C

Animal reproduction studies have not been conducted with VIPLAS/SD. It is also not known whether this product can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity (*see Carcinogenicity, Mutagenicity and Impairment of Fertility).* VIPLA/SD should be given to a pregnant woman only if clearly needed.

CARCINOGENICITY, MUTAGENICITY AND IMPAIRMENT OF FERTILITY

VIPLAS/SD contains no more than 3 µg/mL (ppm) each of TNBP and Triton X-100.

Toxicologic evaluation has confirmed the absence of neoantigens as well as the safety of the TNBP and Triton X-100 that may remain in the final product. Mutagenicity determinations of the TNBP and Triton X-100 *in vitro* and *in vivo* were negative and reproduction toxicity tests have revealed no evidence of embryotoxic or teratogenic properties. No investigations on carcinogenesis or impairment of fertility have been conducted.

ADVERSE REACTIONS

Adverse reactions are similar to those seen with the administration of Fresh Frozen Plasma and may include allergic reactions and dyspepsia. As with the intravenous administration of any product, the following reactions may be observed after administration: headache, fever, chills, flushing, nausea, vomiting, lethargy or other manifestations of allergic reactions. During clinical studies with product, 47 of 396 treatment episodes were associated with adverse events. 74% of these events were allergic reactions, and all of the allergic reactions were of mild to moderate severity and were responsive to treatment with antihistamines such as diphenhydramine HCl. Other adverse events noted were heartburn/epigastric burning (2 patients), and dysgeusia, and tachycardia/irregular heart beat, congestive heart failure and a poorly formed, loose stool in 1 patient each. In FFP-controlled studies, where most patients had previous exposure to FFP, 11/55 (20%) VIPLAS/SD infusions were complicated by an allergic reaction, as were 14/51 (27%) FFP infusions. The studies were underpowered to detect a difference in safety profile between VIPLAS/SD and FFP should such a difference have existed. Equivalence or superiority cannot be inferred from these studies.

If large volumes of plasma are administered, volume overload, citrate toxicity, hypothermia and other metabolic problems may occur. Antibodies in the plasma may react with the recipient's red cells, causing a positive direct antiglobulin test, possibly hemolysis and, rarely, noncardiogenic pulmonary edema [transfusion-related acute lung injury (TRALI)].

DOSAGE AND ADMINISTRATION

VIPLAS/SD should be ABO compatible with the recipient's red cells. The amount of VIPLAS/SD required for normalizing hemostasis will depend upon the patient and upon the circumstances. As a general guideline, it has been reported that plasma levels of between 0.1 and 0.2 u/mL (10% to 20% of normal) of most factors are hemostatic, except for factor XIII where 0.05 u/mL and factor II where 0.3 u/mL are reported to be hemostatic[7]. Therefore, for treatment of a bleeding episode or routine prophylaxis against spontaneous bleeding, the dosage of FFP administered has generally been that calculated to achieve and maintain a plasma concentration of 10% to 20% of normal of the deficient factor. Since a unit of VIPLAS/SD has been demonstrated to increase the level

of individual clotting factors by 2-3% in a normal adult. 4 - 6 units (11 to 17 mL/kg) administered to a 70 kg person should increase factor levels by 8-18%, i.e. 0.08 to 0.18 u/mL. For prophylaxis to cover an invasive procedure, higher plasma levels are targeted, but may not be easily achieved because of volume overload.

For the treatment of chronic TTP, an infused dose of 50-100 mL in children and up to 3 units for adults has been found to be satisfactory at preventing relapses; the dose is repeated as necessary, typically at 3-week intervals. For the treatment of acute TTP, more vigorous treatment is warranted, and exchanges of up to 2 plasma volumes of VIPLAS/SD daily, or as often as deemed necessary, are appropriate.

Do not use the frozen component if there is evidence of container breakage or thawing during storage. Plasma may be thawed at a temperature between 30°C and 37°C in a watertight protective plastic overwrap (if a waterbath is used) using gentle agitation. **Do not refrigerate product once thawed; store thawed product at ambient temperature.**

Administer this product intravenously at room temperature.

VIPLAS/SD should be used as soon as possible after thawing but no more than 24 hours after thawing. **Do not refreeze.** Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Make certain the administration set contains an adequate filter.

HOW SUPPLIED

VIPLAS/SD is supplied frozen in plastic bags each of which contains 200 mL of SD-treated plasma and is labeled with the ABO blood type.

STORAGE

VIPLAS/SD should be stored frozen at -18°C or colder. Storage stability studies reveal maintenance of product coagulation factors when stored for 12 months at -18°C.

Rx only.

REFERENCES

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